Classification Status of Racetams

Reason for Submission

The Ministry of Health has received numerous queries regarding the regulatory position of products used for cognitive enhancement (also referred to as smart-drugs and nootropics), and whether there should be restrictions on their importation into New Zealand. Many of the products are based on a group of compounds known collectively as racetams or 'racetam-like' substances.

Only two of the racetams (piracetam and levetiracetam) are currently classified as prescription medicines in Schedule I of the Medicines Regulations 1984. Medsafe considers it appropriate to similarly classify other racetams and racetam-like compounds that are emerging as having claimed nootropic or other effects on cognitive and central nervous system abilities.

A prescription classification is considered appropriate as the risk profile of the substances has not been extensively studied but is expected to be similar to that of levetiracetam.

Background

Overview of racetams

Racetams are chemically synthesised, not naturally occurring. They share a 2-pyrrolidone nucleus and are derivatives of gamma-aminobutyric acid (GABA), which acts as a major inhibitory neurotransmitter in the brain.

Pyrrolidone nucleus

The first racetam (piracetam) was discovered in the late 1960s. Since then, more than twenty piracetam-like substances have been synthesized and proposed for cognitive improvement or treatment of cognitive impairment and central nervous system disorders. They have broadly been defined as nootropic (from the Greek words *noos* for mind and *tropein* for towards) even though the functions of many of the racetams are not well defined and require further investigation.

The mode of action of these substances is also not well defined. A 2010 review by Malykh & Sadaie[1] suggests differential effects on subtypes of glutamate receptors, but not GABAergic actions.

Despite this lack of clarity, the claimed actions (e.g. to increase memory capacity) mean that the racetams are regarded as medicines.

Current classification status

Two of the racetams are currently scheduled as prescription medicines in New Zealand:

- Piracetam (25th MCC meeting)
- Levetiracetam (27th MCC meeting).

Piracetam was scheduled as a prescription medicine on the basis that it was a new chemical entity. However, the associated new medicine application was subsequently withdrawn, and there are no medicines containing piracetam currently approved.

Several medicines that contain levetiracetam have been approved in New Zealand. These medicines are indicated for use in epileptic patients for the treatment of partial onset seizures.

The other racetams are not currently scheduled in New Zealand under the Medicines Regulations because, although they are analogues of the scheduled racetams, they are not esters or salts of them.

A similar situation exists in Australia.

Examples of racetams

A 2010 review by Malykh & Sadaie[1] identified 15 racetams and divided them into three categories:

- Subgroup 1 (SG1) – those that may have a cognitive enhancement effect e.g. aniracetam, oxiracetam, phenylpiracetam (fonturacetam), piracetam, pramiracetam
- Subgroup 2 (SG2) – those that may have an antiepileptic/anticonvulsive action e.g. brivaracetam, levetiracetam, seletracetam
- Subgroup 3 (SG3) – those with unknown efficacy e.g. coluracetam, dimiracetam, fasoracetam, nebracetam, nefiracetam, rolipram, rolziracetam.

The review describes some of the studies conducted on the above substances, and confirms that they are (or have been) investigated for therapeutic purposes.

An internet search identifies seven others that would fit within subgroup 3. These are cebaracetam, doliracetam, dupracetam, etiracetam (the racemic mixture of levetiracetam and its R enantiomer), imuracetam, nicoracetam and piperacetam.

In addition, three substances that do not strictly meet the racetam definition (due to lack of a 2-pyrrolidone ring) are typically described as being part of the racetam family. These are aloracetam, molracetam and noopept.

The names of the above 25 structures are all International Proprietary Names (INNs). Their chemical structures and International Union of Pure and Applied Chemistry (IUPAC) names are given in Table 1, along with brief descriptions of their uses (where available) from the online edition of “Martindale: The Complete Drug Reference” (accessed 9 January 2015).

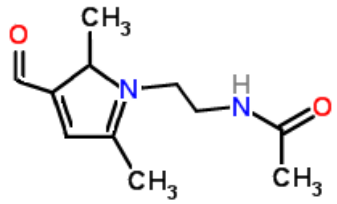
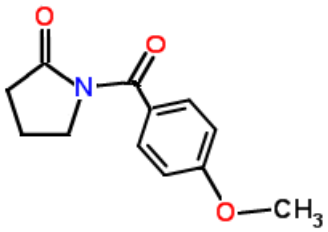
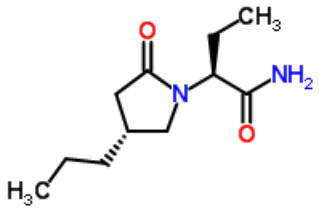
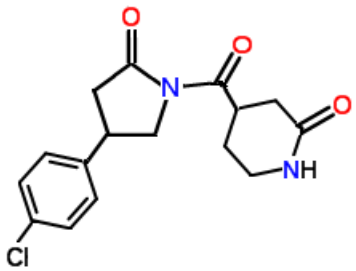
While not described in Martindale or the Malykh & Sadaie review, some of these substances are being used by healthy individuals wanting cognitive enhancement (i.e. smart drugs). Some websites also attempt to compare potency of various racetams against piracetam or levetiracetam. For instance, fonturacetam has been

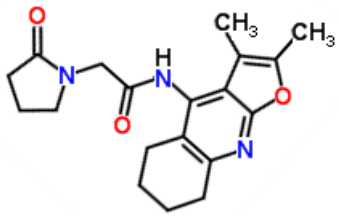
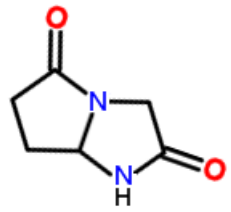
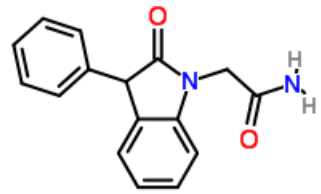
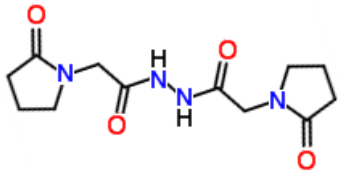
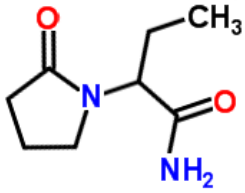
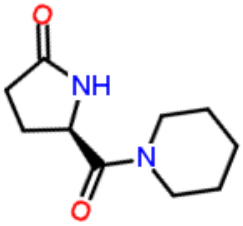
described as 30-60 times more potent than piracetam, noopept has been described as 1000 times more potent than piracetam, and brivaracetam has been described as 10 times more potent than levetiracetam.

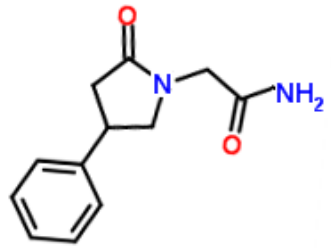
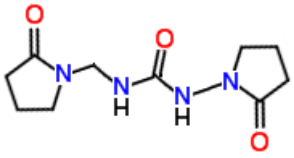
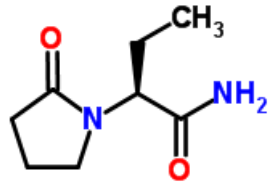
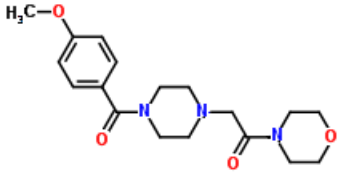
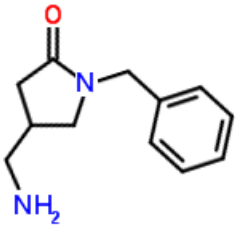
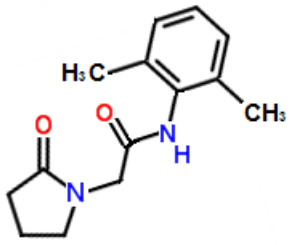
It is clear from the structures and IUPAC names listed in Table 1 that some of these substances may be able to exist in different stereochemical configurations (i.e. the same molecular formula and sequence of bonded atoms but differing in the three-dimensional orientation of the atoms in space). Therefore, for clarity, any scheduling should also include reference to the stereoisomers of these substances.

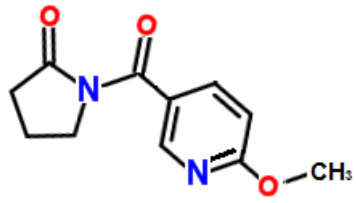
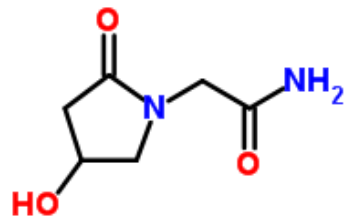
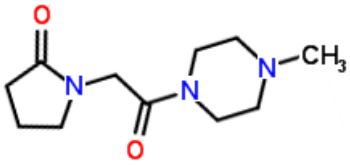
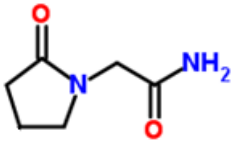
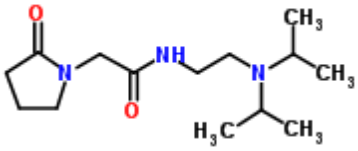
Of the substances listed in Table 1, only levetiracetam is present in approved medicines in New Zealand.

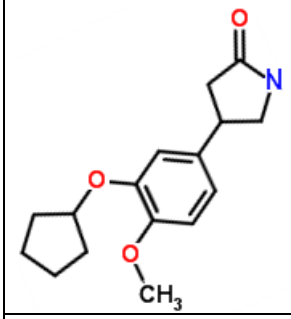
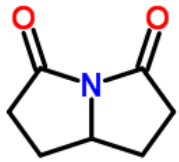
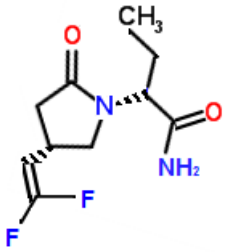
Table 1. Racetam structures

Aloracetam 	Racetam -like	IUPAC name N-[2-(3-formyl-2,5-dimethylpyrrol-1-yl)ethyl]acetamide Reported to be developed for the treatment of Alzheimer's disease, but no indication that it has been approved overseas for this purpose.
Aniracetam 	SG1	IUPAC name 1-[(4-methoxybenzoyl)]-2-pyrrolidinone A prescription medicine in some parts of Europe e.g. Greece (Memodrin and Referan) and Italy (Ampamet). Indicated for mental function disorders.
Brivaracetam 	SG2	IUPAC name (2S)-2-[(4R)-2-oxo- 4-propylpyrrolidin-1-yl] butanamide Developed as a replacement for levetiracetam for preventing seizures, but no indication it has been approved for this purpose overseas.
Cebaracetam 	SG3	IUPAC name 4-[2-[4-(4-chlorophenyl)-2-oxopyrrolidin-1-yl]acetyl] piperazin-2-one

Coluracetam 	SG3	IUPAC name N-(2,3-dimethyl-5,6,7,8-tetrahydrofuro[2,3-b]quinolin-4-yl)-2-(2-oxo-1-pyrrolidinyl)acetamide
Dimiracetam 	SG3	IUPAC name (RS)-3,6,7,7a-tetrahydro-1H-pyrrolo[1,5-a]imidazole-2,5-dione
Doliracetam 	SG3	IUPAC name 2-(2-oxo-3-phenyl-3H-indol-1-yl)acetamide
Dupracetam 	SG3	IUPAC name 2-(2-oxopyrrolidin-1-yl)-N'-[2-(2-oxopyrrolidin-1-yl)acetyl]acetohydrazide
Etiracetam 	SG3	IUPAC name (RS)-2-(2-oxopyrrolidin-1-yl)butanamide Racemic mixture of levetiracetam and its R enantiomer.
Fasoracetam 	SG3	IUPAC name (5R)-5-(piperidine-1-carbonyl) pyrrolidin-2-one

Fonturacetam 	SG1	IUPAC name (R,S)-2-(2-oxo-4-phenylpyrrolidin-1-yl)acetamide Also known as 4-phenylpiracetam. A prescription medicine in Russia (Phenotropil) where it is indicated for metabolic and vascular cerebral disorders, mental function disorders, depression, obesity, convulsions and chronic alcoholism. Also a prescription medicine in the Ukraine (Phenotropil and Entrop) where it is indicated for cerebrovascular disorders and mental function impairment. Listed by the World Antidoping Drug Agency (WADA) as a banned substance because of its stimulant properties.
Imuracetam 	SG3	IUPAC name N,N'-bis[(2-oxopyrrolidin-1-yl)methyl]urea
Levetiracetam 	SG2	IUPAC name (S)-2-(2-Oxopyrrolidin-1-yl)butanamide Prescription medicine in New Zealand.
Molracetam 	Racetam -like	IUPAC name 2-[4-(4-methoxybenzoyl)piperazin-1-yl]-1-morpholin-4-ylethanone
Nebracetam 	SG3	IUPAC name (RS)-4-(aminomethyl)-1-benzylpyrrolidin-2-one Has been investigated as a cognition adjuvant in the treatment of Alzheimer's disease.
Nefiracetam 	SG3	IUPAC name N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide Has been investigated in some cerebrovascular disorders and for the treatment of Alzheimer's disease.

Nicoracetam 	SG3	IUPAC name 1-(6-methoxynicotinoyl)pyrrolidin-2-one
Noopept 	Racetam -like	IUPAC name N-Phenylacetyl-L-prolylglycine ethyl ester Marketed as a medicine in Russia for mental function impairment, brain trauma and asthenia.
Oxiracetam 	SG1	IUPAC name (RS)-2-(4-hydroxy-2-oxopyrrolidin-1-yl)acetamide Marketed as a medicine in Italy under the brand names Neupan, Neuractiv and Neuromet. Indicated for mental function impairment.
Piperacetam 	SG3	IUPAC name 1-[2-(4-methylpiperazin-1-yl)-2-oxo-ethyl]pyrrolidin-2-one
Piracetam 	SG1	IUPAC name 2-(2-oxopyrrolidin-1-yl)acetamide Prescription medicine in New Zealand.
Pramiracetam 	SG1	IUPAC name N-[2-(Diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl) acetamide Marketed as a medicine in Italy (Neupramir, Pramistar and Remen) and the Ukraine (Pramistar). Indicated for mental function impairment.

Rolipram  	SG3	IUPAC name (RS)-4-(3-cyclopentyloxy-4-methoxy-phenyl)pyrrolidin-2-one Has been investigated for antidepressant properties.
Rolziracetam  	SG3	IUPAC name dihydro-1H-pyrrolizine-3,5(2H,6H)-dione
Seletracetam  	SG2	IUPAC name (2S)-2-[(4R)-4-(2,2-difluoroethenyl)-2-oxo-pyrrolidin-1-yl]butanamide Originally developed as a replacement for levetiracetam for anticonvulsant properties, but development appears to have halted.

Conclusion

Piracetam and levetiracetam are already scheduled as prescription medicines in New Zealand. Given the claims being made for the other racetam substances, and the comparisons being made between many of these substances and piracetam or levetiracetam, it is recommended that the other racetam substances also be scheduled as prescription medicines. For clarity, reference to the stereoisomers of these substances (where relevant) should also be included in the scheduling.

Individual entries, rather than a group entry, are recommended at this time to avoid inadvertently capturing other ingredients. This will result in the addition of the following to Schedule 1 of the Medicines Regulations 1984:

> aloracetam, aniracetam, brivaracetam (and its stereoisomers), cebaracetam (and its stereoisomers), coluracetam, dimiracetam (and its stereoisomers), doliracetam (and its stereoisomers), dupracetam, eitracetam, fasoracetam (and its stereoisomers), fonturacetam (and its stereoisomers), imuracetam, molracetam, nebracetam (and its stereoisomers), nefiracetam, nicoracetam, noopept (and its stereoisomers), oxiracetam (and its stereoisomers), piperacetam, pramiracetam, rolipram (and its stereoisomers), rolziracetam, seletracetam (and its stereoisomers).

Attachments

1. Malykh & Sadaie. 2010. *Drugs*. Piracetam and Piracetam-Like Drugs. From Basic Science to Novel Clinical Applications to CNS Disorders. 70(3) 287-312.